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# Nonlinear interactions in a dendritic tree: Localization, timing, and role in information processing

(local circuit/retinal ganglion cell/cable theory)

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ABSTRACT **In a passive dendritic tree, inhibitory synaptic inputs activating ionic conductances with an equilibrium potential near the resting potential can effectively veto excitatory inputs. Analog interactions of this type can be very powerful if the inputs are appropriately timed and occur at certain locations. We examine with computer simulations the precise conditions required for strong and specific interactions in the case of a δ-like ganglion cell of the cat retina. We find some critical conditions to be that (*i*) the peak inhibitory conductance changes must be sufficiently large (i.e., ≈50 nS or more), (*ii*) inhibition must be on the direct path from the location of excitation to the soma, and (*iii*) the time course of excitation and inhibition must substantially overlap. Analog AND–NOT operations realized by satisfying these conditions may underlie direction selectivity in ganglion cells.**

When two neighboring regions of a dendritic tree experience simultaneous conductance changes—induced by synaptic inputs—the resulting postsynaptic potential at the soma is usually not the sum of the potentials generated by each synapse alone. Even though the existence of such nonlinear interactions in a passive dendritic tree has been long recognized, both theoretically and experimentally (1–4), it has been customary to assume linear summation of excitatory and inhibitory inputs on the dendrites and to regard the threshold associated with spike generation at the axon hillock as performing the elementary logical operations in the nervous system. It is, however, possible that synapses situated close to each other on the dendrite of a cell may interact in a highly nonlinear way. For instance, an inhibitory synapse that increases membrane conductance to an ionic species having an equilibrium potential close to the resting potential of the cell has little effect on the potential but may have a powerful influence in offsetting the depolarization induced by neighboring excitatory synapses. This shunting effect is an analog implementation of an AND–NOT operation—one input vetoing the other. Since Barlow and Levick's analysis (ref. 5; see also refs. 6 and 7), it has been well known that the interactions responsible for direction selectivity in rabbit retinal ganglion cells are between local subunits of the receptive field and that they are inhibitory, one channel vetoing the other. In an analysis based on a lumped electrical model of the membrane of the cell, it was suggested (8, 9) that shunting inhibition may be the underlying mechanism for this. The analysis left open the exact conditions required to produce effective and specific nonlinear interactions in a dendritic tree, in particular the location and proximity of the synapses, size of the conductance changes, and morphology of the dendritic branches. We have recently used cable theory to analyze the interaction of excitatory synaptic input with steady-state shunting inhibitory input in various types of cat retinal ganglion cells (10). Nonlinear synaptic interactions were found to be maximal for γ and δ cells and relatively weaker for α and β cells. On the basis of this analysis, we conjectured that cells with a δ-like morphology are the substratum for directional selectivity in the retina. In this note, we wish to show the main properties and critical features of the interaction between transient synaptic inputs for the δ cell shown in Fig. 1*a*, whose geometry was measured from histological (Golgi) material of Boycott and Wässle (11). The main result consists of a set of critical predictions about direction-selective ganglion cells and the organization and properties of their synaptic input.

The branching structure, the length, and the diameters of each dendritic segment were determined as described (10, 12). The dendritic tree was approximated by short segments, each being equivalent to a cylinder. A program using Butz and Cowan's algorithm (13) was used to compute from these data (for a range of values of the membrane capacity $C_m$, membrane resistance $R_m$, and intracellular resistance $R_i$) the linear electrical properties of the cell. We assumed the dendritic membrane to be passive and the spread of current along dendrites to be adequately described by linear cable theory. In the program, the complex transfer resistances $\tilde{K}_{ij}(\omega)$ for any two locations $i,j$ in the dendritic tree are computed. If a current $I_j$ is injected at location $j$, the resulting voltage at location $i$ is given by $V_i(t) = I_j(t) * K_{ij}(t)$, where $*$ indicates convolution and $K_{ij}(t)$ is the inverse Fourier transform of $\tilde{K}_{ij}(\omega)$. The set of $\tilde{K}_{ij}(\omega)$ for various locations $i,j$ characterizes completely the (linear) electrical properties of a branched passive cable.

We considered the case of an excitatory synapse modulating the conductance $g_e$ to an ionic species with equilibrium potential $E_e > V_{rest}$ in location $e$ and an inhibitory synapse modulating the conductance $g_i$ to an ionic species with equilibrium potential $E_i \approx V_{rest} = 0$ in location $i$ (where $V_{rest}$ is the resting potential: for evidence of shunting inhibition in ganglion cells, see refs. 14–18). For inputs consisting of transient conductance changes, the system of Volterra integral equations giving the resulting somatic potential is

$$\begin{aligned} V_s(t) &= \{g_e(t)[E_e - V_e(t)]\} * K_{es}(t) - [g_i(t)V_i(t)] * K_{is}(t) \\ V_e(t) &= \{g_e(t)[E_e - V_e(t)]\} * K_{ee}(t) - [g_i(t)V_i(t)] * K_{ie}(t) \quad [1] \\ V_i(t) &= \{g_e(t)[E_e - V_e(t)]\} * K_{ei}(t) - [g_i(t)V_i(t)] * K_{ii}(t), \end{aligned}$$

where $V_s$, $V_e$, and $V_i$ are the membrane potential at the soma, at the excitatory synapse, and at the inhibitory synapse, respectively. This system of equations was integrated numerically

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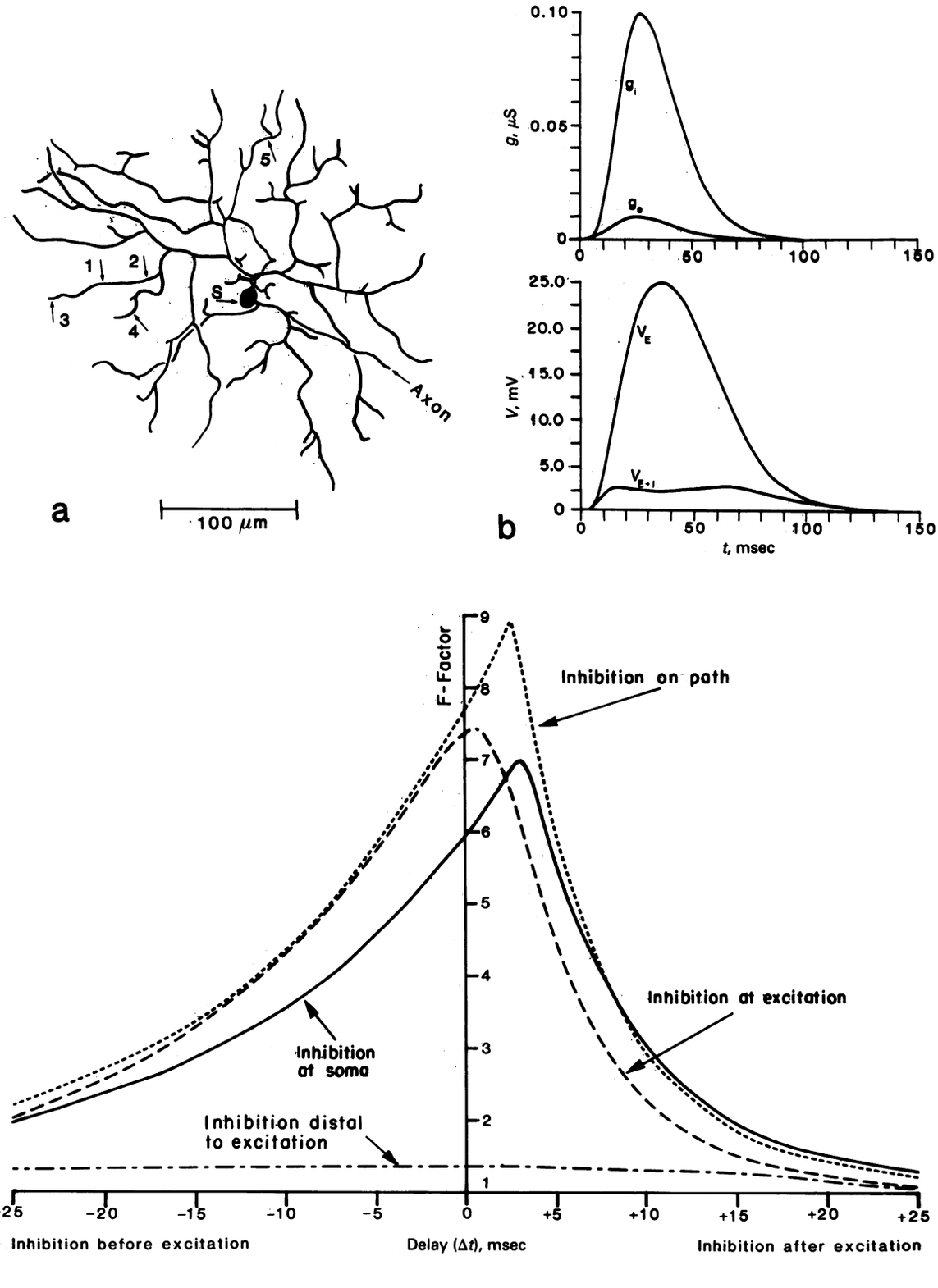


FIG. 1. (*a*) A cat retinal ganglion cell of the δ type (11). In the calculations reported in *b* and *c*, $C_m = 1\ \mu F/cm^2$, $R_m = 14{,}000\ \Omega\cdot cm^2$, and $R_i = 70\ \Omega\cdot cm$. (*b*) The depolarization in the soma of the δ cell of *a* for an excitatory input $g_e$ at location 1 and an inhibitory input $g_i$ at location 2. Both inputs have the time course $g(t) = t^4 \exp(-4t/t_{peak})$ but different peak values—$g_e = 10$ nS and $g_i = 100$ nS. Location and timing of inhibition are optimal (i.e., the inhibition is delayed by 2.5 msec). The excitatory battery is $E_e = 80$ mV and the inhibitory battery is $E_i = 0$ mV (relative to the resting potential). The corresponding somatic depolarization in the absence ($V_E$) and in the presence ($V_{E+I}$) of inhibition are also shown. The maximum of $V$ is for $t = 36$ msec. Since $g(t)$ peaks at $t = 25$ msec, the traveling time from location 1 to the soma is about 11 msec, which equals the phase lag of the transfer function $\tilde{K}_{is}(\omega)$ for $\omega = 0$. Inhibition alone is "invisible" (because $E_i = 0$); its effect appears only when *simultaneous* excitation takes place, as expected for a nonlinear interaction. (*c*) *F* factor (ratio of the maximum of the somatic depolarization without inhibition to the somatic depolarization with inhibition) for various locations of excitation and (shunting) inhibition in the cell of *a* as a function of relative timing.

for given inputs $g_e$ and $g_i$ using the $K_{ij}$ functions calculated by our program for the specific cell. The somatic potential $V_s(t)$ for an excitatory input $g_e(t)$ occurring in the presence or absence of an inhibitory input $g_i(t)$ is shown in Fig. 1*b*.

A simple measure of the effectiveness of shunting inhibition is the ratio ($F$) between the maximum of somatic depolarization in the absence of inhibition and in the presence of the inhibitory input. Eqs. 1 can be solved analytically for steady-state inputs. It is then possible to prove rigorously from general properties of the $K_{ij}$ that (for steady-state inputs) the most effective location for inhibition is always *on the direct path* from the location of the excitatory synapse to the soma (10). The optimal location of inhibition coincides with the location of the excitatory synapse when $g_e$ and $g_i$ are small and moves toward the soma along the direct path when $g_e$ or $R_m$ (or both) increases. When the inhibition is not of the shunting type (i.e., $E_i < V_{rest}$), inhibition at the soma is consistently more efficient. Our numerical solutions of Eqs. 1, some of which are shown in Fig. 1*c*, suggest that the above results, rigorously proved for the steady-state inputs, hold also for transients. The values that we assume for $R_m$, $R_i$, and $C_m$ (see Fig. 1) are within the expected physiological range. The time-to-peak ($t_{peak}$) of the conductance changes were chosen to be consistent with data on retinal ganglion cells, but our results do not depend critically on this.

For $g_i > 50$ nS, $F$ is quite large for on-path inhibition over a wide range of $R_m$ (from 500 $\Omega\cdot cm^2$ to 1 $M\Omega\cdot cm^2$). $F$ increases with increasing $R_m$ but not very steeply (at most by a factor for 3 for $R_m$ increasing 3 orders of magnitude). Over the same $R_m$ range, the "on path" effect maintains good specificity, inhibition in distal locations giving a relatively weak effect. The situation changes for peak values of the inhibitory conductance <50 nS. Two cases must then be distinguished. (*i*) $R_m$ is low: then $F$ is between 1 and 2 (for $R_m$ = 500 $\Omega\cdot cm^2$, $g_e$ = 1 nS and $g_i$ = 10 nS; $F$ = 1.6 under optimal conditions). (*ii*) $R_m$ is larger: then the $F$ values are also larger (for $R_m$ = 20,000 $\Omega\cdot cm^2$ and the above conductance values, $F$ = 2.9). In case *ii*, the neuron is electrically almost equipotential. Then the on-path specificity of inhibition is less and its strength depends mainly on the distance from excitation (especially for small values of $g_e$); for very large values of $R_m$ (around 1 $M\Omega\cdot cm^2$), inhibitory inputs at any location throughout the dendritic tree have very similar effect. For large values of $R_m$, the soma usually becomes the optimal location for inhibition. $F$ values and the on-path specificity are more sensitive to changes in $R_i$, increasing with intracellular resistance. The physiological range of $R_i$ is, however, quite restricted (between 50 and 100 $\Omega\cdot cm$).

Thus, one can envisage that a neuron can work in two different modes of operation, depending on the strength of the synaptic inputs. The interaction between small conductance inputs is mainly a function of the distance between the synapses involved while, for larger inputs, the interaction is more specific, showing a strong on-path effect. An example of the strength of on-path shunting inhibition for the transient inputs is shown in Fig. 1*b*. For the same conductance changes, inhibition on the direct path is strong whereas inhibition behind excitation or on a side branch a few micrometers further away is much less effective.

The way in which the timing of the excitatory vs. the inhibitory input influences the effectiveness of the interaction is shown in Fig. 1*c*. The optimal delay is essentially due to the propagation time of excitation to the location of inhibition. For $t_{peak}$ = 25 msec, on-path inhibition can effectively veto excitation if it occurs within about 10 msec of the onset of the excitatory input. Related effects can be obtained by a longer lasting inhibition (instead of delayed inhibition). Since a shunting inhibition is similar to opening a hole in the membrane, its effect depends on the size of the conductance change and on the time for which it is open. We investigated the effect of changing the $t_{peak}$ of the inhibitory input for a fixed delay between excitation and inhibition. Reducing the $t_{peak}$ for inhibition to less than the fixed value for excitation drastically reduces $F$. Thus, in this example, inhibition must last at least as long as excitation to be effective but does not need to last much longer (depending on location). When the locations of excitation and inhibition coincide, maximal effectiveness of inhibition is reached for a $t_{peak}$ as long as the excitatory $t_{peak}$ whereas inhibition in the soma needs to last roughly twice as long as excitation to be maximally effective.

Because of the strength and specificity of such nonlinear interactions, we propose that they may perform characteristic information-processing operations in passive dendritic trees. Since inhibition vetoes effectively more distal excitatory inputs only when it is on the direct path to the soma, a variety of local operations can be performed, exploiting the branching geometry of a dendritic tree having a suitable localization of excitatory and inhibitory inputs. Timing of inputs provides an additional important control variable: on-path inhibition can veto in an AND–NOT fashion an excitatory input only when it takes place within a well-defined temporal window.

Our results hold also for the more unusual case of an input that decreases conductance for ions in equilibrium near the resting potential (19–21). In this case, the synaptic input facilitates the excitatory effect, thus implementing an analog approximation of a logical AND operation instead of the AND–NOT discussed in this paper. Simple operations of the AND–NOT type may underly, for instance, direction selectivity to motion of certain neurons (5–7); mechanisms of the AND type could be used in other motion-sensitive cells (for instance, in insects).

In summary, we found that in the $\delta$ cell of Fig. 1*a* the veto effect can be (*i*) strong, (*ii*) specific with respect to the relative position of excitation and inhibition, and (*iii*) tuned to their (relative) timing. Properties *i–iii* depend on the electrical parameters and on the morphology of the cell. The following are critical requirements. (*a*) The inhibitory synapse must have an equilibrium potential near the resting potential, while the excitatory synapse must have an equilibrium potential well above it. (*b*) Inhibitory synapses should be more proximal to the soma (on the same dendrite) than excitatory synapses or at the same location; i.e., the on-path property should be satisfied. (*c*) Peak inhibitory conductance changes must be sufficiently large, on the order of 50 nS or larger. (*d*) For maximal effect, inhibition must be at least as long as excitation and their time courses should overlap substantially.

So far as we can tell these predictions are compatible with the available data about direction-selective cells. In particular, recent evidence (17, 22) supports the first point. Histochemical

The conductance inputs are as in *b*, but with various delays between them. Note that the optimal timing for $e = i$ is not for $\Delta t = 0$; the deviation is, however, small. The excitation is always at location 1 (see *a*), while inhibition can be distal to excitation (location 3), coincident with excitation, on the direct path (location 2), or at the soma (location S). For inhibition at location 4 or 5, $F$ is broadly tuned with peak values of 1.69 and 1.5, respectively. The basic results hold over a wide range of parameters: in particular $R_m$ can be increased by several orders of magnitude without a significant change in the direct path property, which depends critically on branching geometry and effective intracellular resistance. Excitation at location 2 and inhibition in other positions give similar qualitative results.

and physiological methods may soon provide evidence in favor of or against the other two conditions. The size of the inhibitory conductance change required by the proposed mechanism is rather large but not unreasonable (the peak amplitude of the conductance change induced by an acetylcholine quantum in the neuromuscular synapse is about 25 nS (see discussion in ref. 10). Although direction selectivity in the retina will probably represent the first critical test for our suggestion, the proposed biophysical mechanism may play a role in other neurons of the central nervous system that do not use dendritic spikes. The retina may represent a somewhat special case because of the importance of graded potentials for internal signaling. Synapses that modulate the conductance of ionic species with equilibrium potential close to the resting potential may veto or facilitate excitatory inputs on a dendritic tree very effectively and specifically. Although we have considered here the case of postsynaptic inhibition, the same veto mechanism can be very effective with presynaptic inhibition (for a specific local circuit, see ref. 23).

Thus, a passive dendritic tree may perform hundreds of independent analog operations on its synaptic inputs without requiring any threshold mechanism. Since all logical operations can be synthetized simply in terms of AND and AND–NOT, simple local circuits consisting of synapses between the dendrites of two or more neurons could implement the analog equivalent of all logical operations (24).

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